

REMARKS/ARGUMENTS:

Claims 32, 35, 36, 59, 60, and 69 are amended. Claims 32, 34-36, 38, 40-45, 55, 58-61, and 63-71 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

The present invention relates generally to gene silencing phenomenon, and particularly to gene silencing using mRNA-cDNA hybrids and methods for generating mRNA-cDNA hybrids for use in gene silencing. (Applicant's specification, at p. 1, lines 6-8).

CLAIM REJECTION UNDER 35 U.S.C. § 112, 1<sup>ST</sup> PARAGRAPH:

Claims 32, 34-36, 38, 40-45, 55, 58-61, and 63-71 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of inhibiting  $\beta$ -catenin expression *in vivo* in selected organs of chicken embryos using a mRNA-cDNA hybrid duplex, does not reasonably provide enablement for a method of inhibiting expression from any target gene using a mRNA-cDNA hybrid duplex. Applicant respectfully traverses this rejection.

The Office states,

"The specification does not enable any person skilled in the art to which it pertains, or with which it is mostly connected, to make and/or use the invention commensurate in scope with these claims."

Applicant respectfully disagrees. The Office cites studies from Parrish and Tuschl to demonstrate the unpredictability in the art associated with the inhibition of gene expression using RNA-DNA hybrid duplexes.

However, Applicant respectfully submits that the findings of Parrish and Tuschl are not relevant to the present invention. Parrish and Tuschl teach that small double-stranded RNA (siRNA) molecules are capable of triggering gene

silencing in mammalian cells. The siRNAs tested in Parrish and Tuschl were double-stranded RNAs approximately 19-25 nucleotide base pairs. With that composition and size range, Parrish and Tuschl teach the unpredictability of the use of short RNA-DNA hybrid duplexes (19-25 base pairs) as gene-silencing effectors. However, neither Parrish nor Tuschl teach or suggest the present invention, which uses long RNA-DNA hybrid duplexes that are larger than 500 base pairs for generation of small gene-silencing effectors. The long RNA-DNA hybrid duplexes of the present invention are NOT gene silencing effectors, whereas the short RNA-DNA hybrid duplexes tested by the Parrish and Tuschl are directly used as gene-silencing effectors. In view of these totally different standards, the findings of Parrish and Tuschl are irrelevant to the predictability/enableness of the present invention.

As described in the Applicant's specification and the previously cited Grant, S.R. paper (*Cell* 96, 303-306, 1999), the present invention relates to a post-transcriptional gene silencing (PTGS) phenomenon that requires the activity of RNA-directed RNA polymerase (RdRp) on a DNA-RNA hybrid duplex template. This mechanism is namely DNA-RNA interference (D-RNAi) in the present invention. RdRp is an RNA polymerase, which usually transcribes single-stranded antisense RNA from a sense RNA template. Furthermore, in FIG 6 and Example 10 of Applicant's specification, Applicant has provided evidence to prove that the D-RNAi mechanism requires the RdRp activity for generation of small gene-silencing effectors. However, neither Parrish nor Tuschl teach or suggest the requirement of RdRp in their methods. In fact, Parrish and Tuschl teach the requirement of Dicer rather than RdRp in the generation of siRNAs. Dicer is an RNaseIII enzyme which specifically cleaves double-stranded RNAs (dsRNA) into small siRNAs. Therefore, there is no need for the RdRp activity in their methods. Given that RdRp only

transcribes single strand RNAs rather than double-stranded RNAs, the RNaseIII involved in the cleavage of the RdRp-transcribed RNAs must be specific to single-strand RNAs rather than double-stranded RNAs. Applicant respectfully submits that the Office's belief that Dicer and/or siRNA are involved in the present invention is not correct. In particular, the siRNA-associated Dicer cannot even cleave a DNA-RNA hybrid duplex. Therefore, the method and mechanism of Parrish and Tuschl are irrelevant to the predictability/enablement of the present invention.

The claims, as clarified, are directed to a method for inhibiting the expression of a target gene through a post-transcriptional gene silencing (PTGS) mechanism in a cell or organism that expresses the targeted gene. Evidence for this PTGS mechanism has been shown in the Applicant's specification, FIGS. 4 and 6 and Examples 8, 10 and 11. Applicant notes that, as stated in the MPEP at 2164.01(b), as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied.

The MPEP at 2164.01(b) states,

"As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), cert. denied, 484 U.S. 954 (1987)."

In view of the foregoing, Applicant respectfully submits that claims 32, 34-36, 38, 40-45, 55, 58-61, and 63-71 are enabled.

Furthermore, it will also be readily recognized by one of ordinary skill in the art that it is not necessary for one to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect. Therefore, the Office's argument that the claims lack enablement because the art is unpredictable with respect to the limitation of its novel mechanism is not correct.

Applicant respectfully reminds the Office that the purpose of the enablement requirement is for the patent specification to allow the interested public to make and use the claimed invention, not to enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.

The MPEP at §2164 states,

"The purpose of the requirement that the specification describe the invention in such terms that one skilled in the art can make and use the claimed invention is to ensure that the invention is communicated to the interested public in a meaningful way. The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. However, to comply with 35 U.S.C. 112, first paragraph, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect."

Applicant further notes that to make and use the claimed invention, one needs to know how to i) construct a DNA-RNA hybrid duplex (Examples 2-6, 9 and 11, and FIGS 1 and 7); and ii) how to use the DNA-RNA hybrid duplexes and measure the resulting gene silencing effects (Examples 7, 8 and 10, and FIGS 2, 3, 5, 6 and 8-10). Applicant's specification has provided ample guidance on the design, construction and utilization of such a DNA-RNA hybrid duplex construct. The methods of RNA-PCR and DNA transfection into targeted cells are also exemplified in the Applicant's specification and are considered routine in the art.

While there might be experimentation required with regard to the exact reagents, conditions, etc., such experiments are routine in the art of molecular biology. Hence, no undue experimentation is required to practice a method according to the amended claims.

In conclusion, claims 32, 34-36, 38, 40-45, 55, 58-61, and 63-71 satisfy the enablement requirement. Applicant respectfully requests that the final rejection of the claims be reversed and claims 32, 34-36, 38, 40-45, 55, 58-61, and 63-71 be determined to be allowable.

Applicant believes the foregoing amendments comply with requirements of form and thus may be admitted under 37 C.F.R. § 1.116(b). Alternatively, if these amendments are deemed to touch the merits, admission is requested under 37 C.F.R. § 1.116(c). In this connection, these amendments were not earlier presented because they are in response to the matters pointed out for the first time in the Final Office Action.

Lastly, admission is requested under 37 C.F.R. § 1.116(b) as presenting rejected claims in better form for consideration on appeal.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (310) 785-4600 to discuss the steps necessary for placing the application in condition for allowance.


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If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,  
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